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TWO CASES OF EPIDERMOLYSIS BULLOSA.

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ATTENTION was first called in 1882 by Goldscheider* to the rare cutaneous affection of which two cases are reported in this article. He described it as an hereditary predisposition to bullous eruptions, having observed its occurrence in a patient whose father and grandmother on his father's side and her two brothers had been similarly affected. The patient had also a brother and sister who suffered from the same trouble, and also two nieces, children of his sister. Valentin,† in 1885, reported the second case, and found that the process had occurred in eleven persons in four generations of the same family. Köbner,‡ in 1886, recorded the third case, in which the heredity was traced back only one generation to the boy's mother, and he gave to the affection the name still attached to it of "epidermolysis bullosa hereditaria." Other examples of the condition have since been placed on record by Legg, Max Joseph and others, the latter's case being a primary one in the sense that she was the first member of her family to show its evidences. Three children to whom she gave birth, and who suffered from the process

* Goldscheider, *Monatsh. f. prak. Dermat.*, 1882.
† Valentin, *Berlin. klin. Wchsft.*, 1885.
‡ Köbner, *ibid.*, 1886.

from early infancy, testified, however, to the hereditary tendency of the affection.

The two cases which I report here correspond in every particular to those already recorded, and may serve to increase the small number of similar examples to be found in dermatological literature. They are, besides, the only ones so far recorded in this country, and one of them (Case II) gave no hereditary origin for its existence.

Case I. Male, aged thirty, born in this country of German parentage, was seen by me in August, 1892. He was well developed physically and in good functional health. He gave no history of any antecedent diseases beyond the ordinary ones of childhood and slight temporary indispositions. He stated, however, that his father had been affected in a similar way as himself, the cutaneous trouble having developed during our civil war, and apparently in consequence of long and severe marching. The father's trouble was limited to the feet and developed especially in summer after walking, or after pressure or rubbing. The patient was born some years after the existence of the process in the parent, and its primary development was observed when he was five years of age. The manifestations of the affection were not, however, in him limited to the feet, but appeared also on the hands. They were noticed especially in summer, but also occurred at all seasons of the year. The bullous elevations arose without precedent redness, after pressure or rubbing of the hands and feet, after walking or rowing, or after using some instrument or other, a hammer, screw-driver, etc., but not under other circumstances. The patient complained also that in summer he suffered much from hyperidrosis of the hands and feet, and that a bromidrosis of the latter often developed, even the contents of the bullæ being offensive. No subjective symptoms were mentioned, except pain after the bullæ had ruptured and left a raw surface.

When the patient came under observation, there were numerous bullæ of all sizes on the hands and feet, some of which had arisen on the latter during his walk to the consultation. The lesions were prominent, distended, not surrounded by any zone of redness, and were resistant and difficult of rupture. He remained under observation for two months, during which time a succession of bullæ developed whenever in any way the hands and feet were subjected to pressure or rubbing, and all treatment made use of was of no avail in removing the inherent proclivities of the tissues to the formation of the lesions.

Case II. Male, aged twenty-one, born in Germany, was seen by me in June, 1893. His physical development and general and func-

tional health were good in every way. His cutaneous trouble had existed ever since he could remember, and, though he has ten brothers and sisters, neither any of them, nor his parents, nor any of his immediate relations are similarly affected. The lesions developed especially in summer, and appeared on any portion of the body subjected to rubbing or pressure. Bullæ developed upon the hands or feet, around the waist from the rubbing of his suspenders, or upon any surface rubbed for some minutes. He was an instrument-maker by trade, and he was intensely interfered with in his work by the bullous lesions which constantly developed upon his hands whenever he attempted to do anything. They arose without precedent redness or subjective symptoms, and caused pain only after having been ruptured. At the time he consulted me, there were numerous bullæ on his hands and feet, on both the palms and soles and dorsi, and also on his shoulders, around his waist, and here and there where pressure had been applied. The bullæ varied in size from a large pea to a nut; they were tense, and filled with clear serum, and ruptured with difficulty. After they had been broken, the raw surface healed rapidly without pigmentation or other change. Excessive general hyperidrosis was also complained of. The patient remained under observation for several months, and the development of numerous new bullæ was noted at each visit, but no form of treatment devised, either externally or internally, appeared to exert the slightest influence in controlling the condition. He was *in statu quo ante* when last seen.

These two cases may be said to present clinically the features and symptoms characterizing the process of epidermolysis bullosa, but in the one the hereditary influence was traceable, while in the other it was not. We can not, however, exclude the latter or second case from the same category, inasmuch as it agrees with Joseph's case, which was also a primary one, and, besides, for a disease to be hereditary even, there must be and must have been some starting point, some individual who primarily developed it and transmitted it to his descendants. We can not suppose that the tendency must have always existed through an infinite series of the past generations of the ancestors of an affected person, and we are justified in supposing that an individual himself, just as well as some remote progenitor, may originate the predisposition to the condition and then transmit it to his posterity. The patient in question was unmarried and had as yet no children—so, in consequence, no proof of its tendency to become hereditary could be obtained from that source; but nevertheless the clinical picture and course of the affection in Case II were sufficiently characteristic to allow its being regarded as one of epidermolysis bul-

losa similar to Case I, which was hereditary in origin. In this latter there are some features of peculiar interest in Case I to be mentioned. These were the age at which the process developed in the father, the circumstances under which it originated, and its limited and localized character.

Instead of beginning in early childhood, as did all other cases, we find that the tendency to the development of the bullæ only arose after the arduous marching entailed by war service upon the father, he having been previously free from any such symptoms. The disposition once started remained limited to the feet—that is, to the portions of the body primarily affected; but in the son we find that an extension to the hands had occurred, and upon these pressure or rubbing produced the immediate formation of bullæ. This curious feature in the case I will not attempt to speculate upon, inasmuch as we know so little concerning the real influences and factors controlling heredity, but it certainly is important enough for attention to be specially directed to it. Another observation made in the case is also of interest, and that is the hyperidrosis of those surfaces affected in the son. In Case II we find also that hyperidrosis was a prominent feature. In this patient, the sweating was general, not local, and the bullous formations likewise occurred on any part of the body so affected, so that a connection between the hyperidrosis and the cutaneous changes was certainly strongly suggested, especially when we remember that in all cases reported excessive sweating has been mentioned as a marked feature, and that the severest symptoms occurred during the summer, when the tendency to hyperidrosis was naturally increased.

At one of the consultations of Case II a bulla as large as a buckshot, tense, and filled with clear serum, was excised from the inner surface of the left ankle. It had developed during his walk to the clinic, and could not have been present more than one hour before excision. The bulla was fixed in Fleming's solution and hardened in alcohol, then soaked in celloidin and mounted. The sections were stained with hæmatoxylon, borax-carmine, safranin, and the methylene blue neutral orcein method of Unna.

The external envelope of the bulla was found to be composed of the stratum corneum and a large portion of the stratum epitheliale of the epidermis, while at the base portions of the latter were found adherent and forming a more or less continuous or broken layer. Toward the lateral margins of the cavity there could distinctly be seen epithelial columns forming septa, which extended from the outer wall to the base. The contents of the bulla were granular, with fibrin fibers

and shreds distributed through it, but yet no leucocytes or cellular forms whatever.

When the sections were magnified with higher powers, the stratum corneum was found to be unchanged. That portion of the stratum

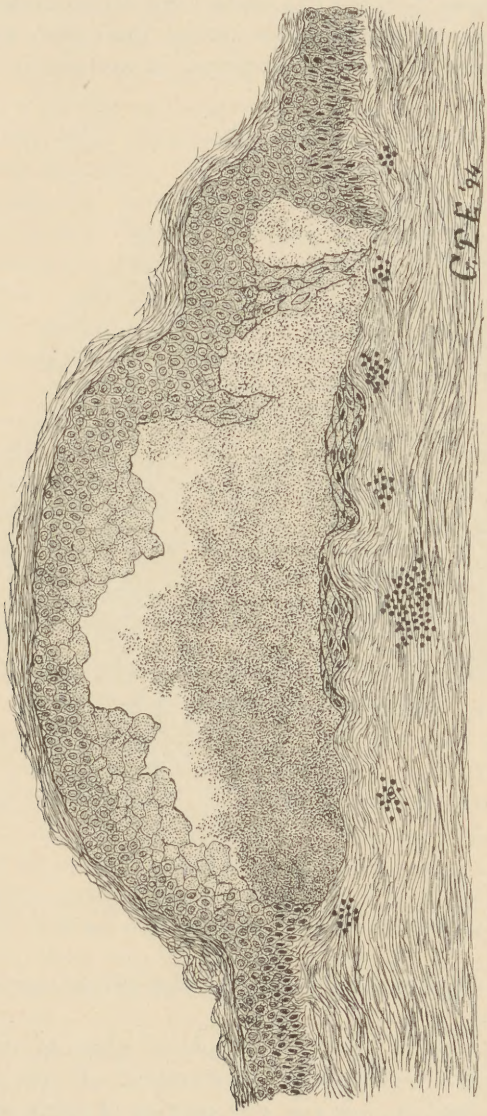

Fig. 1.—Vertical section through a bulla, showing the degenerated portion of rete forming outer wall and masses of rete cells remaining attached to the papillæ. Here and there in the cutis masses of cells around the blood-vessels.

epitheliale, which formed the external envelope of the bulla, was composed of cells granular in aspect, with nuclei staining only slightly or

not at all, and its lower edge was fringed with spaces much larger than normal cells, having a granular appearance and no nuclei (Fig. 1). The nuclei in the entire stratum had the aspect of being soaked in the serous exudation and bereft of their staining characteristics. The epithelial masses forming the septa were degenerated in the same way, though here and there a few nuclei were seen which stained darkly. The same features were observed in connection with the epi-

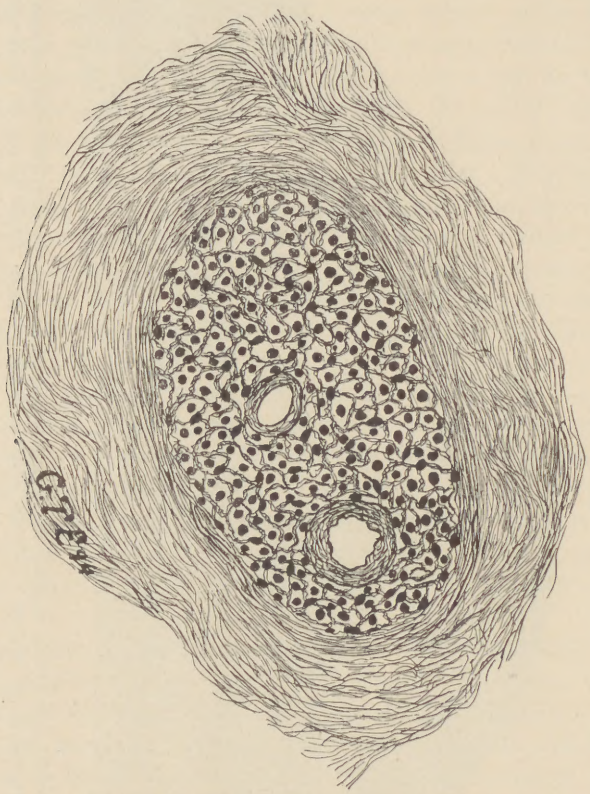

FIG. 2.—Cross section through an artery and vein in the subpapillary portion of the cutis, showing infiltration in œdematous tissue meshes.

thelial remnants situated at the base of the bullous cavity and seated upon the corium.

For some distance beyond the peripheral edges of the bulla itself, the rete presented a very peculiar appearance. It was in no part detached from the papillæ, nor was any portion of itself so separated as to form a cavity—it was intact—but the cells composing its lower third were elongated, their protoplasm granular, the nuclei linear, the

whole giving the appearance of the cells being drawn out longitudinally and compressed laterally. The nuclei of the lowest portions here of the cells of the rete stained deeply, but those in the upper two thirds were either faintly stained or not at all. Karyokinetic figures were not observed in the rete cells. The papillary portion of the corium forming the base of the bullous cavity was either bare, the papillæ jutting into the space nakedly, or, as mentioned, they were covered with a portion of the stratum epitheliale. They were swollen and œdematous, their blood-vessels greatly dilated, but unsurrounded by any cellular elements. In the subpapillary plexus, the dilatation of the blood-vessels was also seen, but around them considerable cellular infiltration occurred. (Fig. 2.) The perivascular tissue was œdematous, and in its meshes the leucocytes were congregated. An increase in the connective-tissue cells was also noted. This perivascular infiltration occurred particularly about the subpapillary plexus, but yet it also extended downwards along the ascending branches of the arterioles almost to the subcutaneous plexus of vessels. There were not, however, any evidences of diffuse cellular infiltration, but this latter was localized around the blood-vessels alone. The lymph spaces of the cutis were likewise dilated, and the whole upper half of the corium was so drenched by the exudation that even the infiltration and fixed cells were stained poorly and with difficulty. The appendages of the skin were normal to all appearances, except the coiled glands. These were, in the region of the coils, surrounded by some cellular infiltration, and the coils themselves were considerably disorganized. The regular arrangement of their cubical epithelium was not found, but the lumina of the coils were filled with nuclei staining faintly or well, and apparently imbedded in granular masses. They were not, however, dilated.

The microscopic examination of the lesion from this case of epidermolysis bullosa thus shows the process to be characterized by a very marked dilatation of the papillary and subpapillary vessels, a soaking of the corium by an excessive serous transudation, and an infiltration of cellular elements about the blood-vessels last mentioned, as well as the ascending branches of the vascular tree. The fluid pouring out so abundantly drenched the upper half of the corium and naturally invaded the rete and led to the cellular changes and the formation of the bulla. It is in view of the deep situation of this lesion in the rete and the absence of the trabecular formations usually occurring in similar lesions, originating slowly and from the amount of inflammatory exudation ordinarily taking place that I would judge that the fluid exudation was sudden and excessive. These epithelial trabeculæ did occur, it is true, at the periphery of the bullous cavity; but in the presence

of the conditions mentioned as existing in the rete beyond the margins of the bulla, it would appear to me that they were only the result of a lateral extension of the original primary bulla, and developed after the acute and excessive amount of transudation had occurred. The splitting off of the rete so deeply in the stratum spinosum does not appear to me to be of any such major consequence as other observers have regarded it, but it seems to me to be determined by the amount of exudation taking place, and also and especially by the macerated condition of the epidermis as a whole, which could result from the hyperidrosis signalized as an important feature in all the cases which have been reported.

The inflammatory infiltration present in the cutis about the blood-vessels is certainly of importance, owing to the fact that such symptoms are not mentioned by others, and it seems to me that they constitute the real pathological features of the process—that is, the finding, in so recent a lesion as was excised in this case, of such extensive perivascular inflammatory infiltration would lead me to regard the process as fundamentally an inflammatory one, in which the bullous formation is simply a consequence of the sudden and excessive serous exudation in an individual with an acquired or hereditarily exaggerated irritability of the cutaneous vascular system. That the objective lesion in these cases is only a result of a mechanical tearing away of the rete by the sudden rush of fluid would seem to me to be apparent from the presence of the changes in the cutis and the absence of any cellular elements in the contents of recent bullæ, or of mitoses in the rete. Most certainly the conditions in the corium were too distinct and marked to allow the single conclusion to be made that the process was alone due to predisposition to a facile solution in continuity of the stratum spinosum, resulting from an exudative condition (Köbner, Goldscheider, etc.). Valentin alone regarded his case as a dermatitis bullosa, though Unna, in his recent work on *Histopathology* of the Skin, regards the process also as a dermatitis, one traumatic in origin. I would unhesitatingly agree with that opinion, and from my pathological study would regard the affection as due in a predisposed individual to an excessive response on the part of the blood-vessels to an external irritation and the consequent pouring out of an enormous amount of serous exudation. The fluid penetrates rapidly into the rete, already somewhat softened and macerated by the hyperidrosis existing, and, tearing it away at its least strong portion, forms then the bulla. The serous exudation is, however, so sudden and rapid that it outstrips the cellular infiltration of the tissue, and, therefore, clinical symptoms of inflammation are wanting at the time the bulla

is formed, and its histological evidences are found only around the blood-vessels when a recent lesion is examined. The same conditions are clinically and histologically present in other diseases—pemphigus, impetigo contagiosa bullosa, etc.—characterized by excessive exudation, when very young and recent lesions are examined, without, however, they being regarded as simply due to facile solution in continuity of the stratum spinosum, or other portion of the rete, and I would, therefore, claim for "epidermolysis bullosa" a more complex pathological nature than has been ascribed to it, and regard it as a dermatitis—that is, as an inflammatory process originating in the cutis itself, and manifesting itself by the formation of bullæ after slight or severer traumatisms.

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